

PATENT COOPERATION TREATY

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24. Nov. 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

To:

ROCHE VITAMINS LTD
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SUISSENOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

22.11.2004

Applicant's or agent's file reference
Case 21364

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/08867 ✓International filing date (day/month/year)
09.08.2003Priority date (day/month/year)
16.08.2002Applicant
DSM IP ASSETS BV

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 21364	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/08867	International filing date (day/month/year) 09.08.2003	Priority date (day/month/year) 16.08.2002
International Patent Classification (IPC) or both national classification and IPC C07C29/42		
Applicant DSM IP ASSETS BV		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 4 sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 2 sheets.
3.	This report contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 18.02.2004	Date of completion of this report 22.11.2004
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized Officer Bedel, C Telephone No. +49 89 2399-2506



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08867**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-8 as originally filed

Claims, Numbers

1-11 received on 14.09.2004 with letter of 09.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08867**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

The amendments filed with letter dated 9-09-04 are in conformity with the requirements of Article 34-b) PCT.

The present application now concerns a process for the preparation of acetylenically unsaturated alcohol by reacting a carbonyl with acetylene in the presence of NH_3 and an **aqueous** alkali metal hydroxide, the carbonyl being chosen among a restricted list (see new claim 1, former claim 4), the molar ratio between the alkali metal hydroxide and the carbonyl compound being less than 1:200.

The term "aqueous" is supported by the passage of the description page 5, I.5-13 as well as all the examples.

- D1: R.J. TEDESCHI: "Base-Catalyzed reaction of Acetylene and Vinylacetylenes with Carbonyl Compounds in Liquid Ammonia under Pressure" J. ORG. CHEM., vol. 28, 1963, pages 1740-1743, XP002264209
- D2: EP-A-1 256 560 (BASF AG) 13 November 2002 (2002-11-13)
- D3: US-A-3 709 946 (MOORE G ET AL) 9 January 1973 (1973-01-09)
- D4: FR-A-2 236 822 (INST ORCH KHIM) 7 February 1975 (1975-02-07)

All the above mentioned documents also disclose a process for making an acetylenically unsaturated alcohol from a carbonyl compound and acetylene in the presence of NH_3 and an alkali metal hydroxide. All the examples in D1-D4 disclose in the examples a ratio above 1:200.

However, although D3 contemplates the use of a large range of ratio (i.e. from 1:1000 to 1:2), none of the cited documents encompasses the use of **aqueous** alkali metal hydroxide as a catalyst.

All the disclosed processes use in fact powdered metal alkali hydroxide sometimes solved in alcohol and show inferior conversion rates compare to the present process. In D4 there is even a prejudice against the use of aqueous alkali because a prior art cited in D4 uses aqueous alkali (albeit with a ratio over 1:200) which poses some technical problem that D4 intended to solve.

Furthermore, the applicant provided some comparative tests (STIN annexed to the present report), that show a significative decrease in diol by-product when using a OH/carbonyl ratio under 1:200.

Therefore the subject matter of claim 1 and dependent 2-11 comply with the requirements of Article 33(2) and (3) PCT.

Application No. PCT/EP 03/08867; Case 21364 WO**Comparative Testing Report****General experimental procedure**

This was a procedure analogous to that described in Example 1 of the present patent application, whereby the molar ratio of the used alkali metal hydroxide (potassium hydroxide, KOH; used as a 45% wt./wt. solution) to the starting carbonyl compound was set at a particular value in each experiment. As in Example 1, the acetylene was added to provide a fixed total pressure for each ethynylation investigated, and the proportion of acetylene in the mixture of ammonia and acetylene was always about 21% (wt./wt.). The reaction duration was in each case either one hour or two hours, and throughout the reaction a temperature of 30°C was maintained. To isolate the product the ammonia was evaporated off at the termination of the one/two hour(s) (1 h / 2 h) reaction duration and the residue in the reaction vessel (2 l autoclave) was acidified with 8% sulphuric acid and then washed with water at 60°C, the pH being maintained at 7. Gas chromatographic analysis of the product enabled the determination of the percentage conversion of the starting carbonyl compound into the acetylenically unsaturated alcohol product, and the determination of the percentage yield of said product and of the unwanted diol by-product based on the aforementioned percentage conversion.

The results for the five ethynylations investigated in the above manner are presented as follows:

Ethynylation 1:	6 methyl-5-hepten-2-one (MH) to dehydrolinalool (DLL)
Ethynylation 2:	hexahydropseudoionone (HPI) to 3,7,11-trimethyl-1-dodecyn-3-ol (TMDO)
Ethynylation 3:	6,10,14-trimethyl-2-pentadecanone (TMPO) to dehydroisophytol (DIP)
Ethynylation 4:	methyl ethyl ketone (MEK) to 2-ethyl-3-butyn-2-ol (EBO)
Ethynylation 5:	6-methyl-5-octen-2-one (MOO) to ethyl dehydrolinalool (EDLL)

The full chemical names of the above-mentioned compounds with "trivial" names, i.e. "dehydrolinalool", "hexahydropseudoionone", "dehydroisophytol" and "ethyl dehydrolinalool", are given on pages 3 and 4 and/or in the Examples of the present patent application.

In the following table of results "KOH : SM" means the molar ratio of the KOH to the starting material (SM), viz. the respective starting carbonyl compound. The ratios greater than 1 : 200, i.e. 1 : <200, such as 1 : 31, 1 : 27 etc., are applicable to the comparative procedures which are not in accordance with the claimed invention, whereas those ratios which are less than 1 : 200, i.e. 1 : >200, such as 1 : 250, are applicable to the comparative procedures which are in accordance with the claimed invention.

Table of results

Ethynylation	KOH : SM	Reaction duration / pressure	Conversion	Product yield	By-product (diol) yield
1: MH → DLL	1 : 31	1 h/16.1 bar	98%	91.9%	3.6%
	1 : 250	1 h/16.1 bar	95.9%	92.9%	1.4%
	1 : 250	2 h/16.1 bar	97.5%	94.3%	1.5%
2: HPI → TMDO	1 : 27	1 h/16.3 bar	97.9%	94.1%	2.5%
	1 : 250	1 h/16.3 bar	96.0%	93.7%	0.6%
	1 : 250	2 h/16.3 bar	96.9%	94.2%	0.6%
3: TMPO → DIP	1 : 24.5	1 h/16.8 bar	97.7%	94.7%	2.0%
	1 : 250	1 h/16.8 bar	95.7%	93.3%	0.6%
	1 : 250	2 h/16.8 bar	97.2%	94.6%	0.6%
4: MEK → EBO	1 : 90	1 h/16.0 bar	99.7%	97.6%	1.6%
	1 : 360	1 h/16.0 bar	97.1%	96.3%	0.4%
5: MOO → EDLL	1 : 46	1 h/16.1 bar	97.9%	94.4%	1.9%
	1 : 250	1 h/16.1 bar	96.5%	93.9%	0.8%
	1 : 250	2 h/16.1 bar	97.7%	95.0%	0.9%

Conclusions from the above results

The tabulated results show above all that in using relative amounts (molar ratios) of alkali metal hydroxide to the starting carbonyl compound which are less than 1 : 200 (claimed invention) compared with relative amounts which are greater than this (state of the art) the amount (yield) of unwanted diol by-product is considerably less, i.e. well under 50%, down to about 25%, of the yield for the respective state of the art procedures.

Claims

1. A process for the manufacture of an acetylenically unsaturated alcohol by reacting a carbonyl compound with acetylene in the presence of ammonia and an alkali metal hydroxide, characterized in that the carbonyl compound is methyl ethyl ketone, methylglyoxal dimethylacetal, 6-methyl-5-hepten-2-one, 6-methyl-5-octen-2-one, hexahydropseudoionone, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one or 6,10,14-trimethyl-2-pentadecanone, the alkali metal hydroxide is used in aqueous solution and the molar ratio of the alkali metal hydroxide to the carbonyl compound is less than 1 : 200.
2. A process according to claim 1, wherein the molar ratio of the alkali metal hydroxide to the carbonyl compound is from about 1 : 500 to 1 : 200.
3. A process according to claim 2, wherein the molar ratio of the alkali metal hydroxide to the carbonyl compound is from about 1 : 300 to about 1 : 220.
4. A process according to any one of claims 1 to 3, wherein the carbonyl compound is 6-methyl-5-hepten-2-one and the product is dehydrolinalool.
5. A process according to any one of claims 1 to 4, wherein the alkali metal hydroxide is potassium hydroxide.
6. A process according to any one of claims 1 to 5, wherein the reaction is effected at a temperature from about 0°C to about 40°C and the pressure is at an appropriate value, depending on the reaction temperature, from about 5 bar to about 20 bar (about 0.5 MPa to about 2 MPa) to maintain the ammonia in the liquefied state.
7. A process according to claim 6, wherein the reaction is effected at a temperature from about room temperature to about 35°C.
8. A process according to any one of claims 1 to 7, wherein the molar ratio of the acetylene to the carbonyl compound in the reaction mixture for carrying out the process is from about 2 : 1 to about 6 : 1.

9. A process according to any one of claims 1 to 8, wherein the molar ratio of ammonia to carbonyl compound in the reaction mixture for carrying out the process is from about 8 : 1 to about 35 : 1.

10. A process according to claim 9, wherein the molar ratio of ammonia to carbonyl
5 compound in the reaction mixture for carrying out the process is from about 10 : 1 to about 30 : 1.

11. A process according to any one of claims 1 to 10, wherein the reaction is effected in a continuous manner.
